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Progestogen-only contraceptive use among breastfeeding women: a systematic review

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Abstract

Background: Postpartum women need effective contraception. Concerns have been raised that use of progestogen-only contraceptives (POCs) may affect breastfeeding performance and infant health outcomes.

Objectives: We investigated the clinical outcomes of breastfeeding duration, initiation of supplemental feeding and weaning, as well as infant outcomes including infant growth, health and development among breastfeeding women using POCs compared with breastfeeding women not using POCs.

Search strategy: We searched the PubMed database for all articles published from database inception through December 2014.

Selection criteria: We included primary research studies of breastfeeding women of any age or parity who received POCs, including progestogen-only pills, injectables, implants or hormonal intrauterine devices (IUDs). The main outcomes were breastfeeding performance (as measured by initiation, continuation, frequency and exclusivity of breastfeeding) and infant health (as measured by growth, development or adverse health effects).

Results: Forty-nine articles reporting on 47 different studies were identified that investigated the use of POCs in breastfeeding women and reported clinically relevant outcomes of infant growth, health or breastfeeding performance. Studies ranged from poor to fair methodological quality and generally failed to show negative effects of the use of POCs on breastfeeding outcomes or on infant growth or development. One randomized controlled trial (RCT) raises concerns

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that immediate insertion of the levonorgestrel IUD postpartum may be associated with poorer breastfeeding performance when compared with delayed insertion, although two other RCTs evaluating early etonogestrel implants compared with delayed initiation of implants or depot medroxyprogesterone acetate failed to find such an association.

Conclusion: The preponderance of evidence fails to demonstrate adverse breastfeeding outcomes or negative health outcomes in infants such as restricted growth, health problems or impaired development. Evidence newly added to this review was largely consistent with previous evidence.

Keywords

Lactation; Contraception; Progestogens; Breastfeeding

1. Introduction

The benefits of breastfeeding for both women and their infants are considerable [1–3]. The World Health Organization (WHO) recommends infants breastfeed exclusively during the first months of life [4]. Although women breastfeeding exclusively and on demand are unlikely to conceive before 6 weeks postpartum, many women discontinue fully breastfeeding before that time and are at risk of repeat pregnancy [5]. Because birth spacing has demonstrated health benefits for women and infants, early initiation of contraception in the postpartum period may improve outcomes.

Progestogen-only and progesterone contraceptives have been in use for years; however, their dosages and formulations have changed over time. Methods available include progestogen-only pills (POPs), progestogen and progesterone implants, injectables, progesterone rings and progestogen-releasing intrauterine devices (IUDs). They are highly effective when used as directed [6].

The use of progestogen-only methods of contraception [progestogen-only contraceptives (POCs)] during the period of lactation has raised concerns for negative effects [7]. Progestogens could interfere with lactogenesis, especially immediately postpartum [8], and have been shown to be transferred to breast milk [9]. Animal data suggest that progesterone receptors are common in the developing rat forebrain [10]. It is therefore possible that POCs may affect infant health or development [11]. The large loading dose of progestogens found in the injectable depot medroxyprogesterone acetate (DMPA) has been particularly called into question [7].

This systematic review was conducted for the WHO's Medical Eligibility Criteria for Contraceptive Use (MEC) [12] and examines the effects of POCs on outcomes such as breastfeeding performance and infant growth, development and health. It updates a previous review from 2010 [13].

2. Methods

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the conduct of systematic reviews. [14]

2.1. Key questions

We identified two key questions of interest: (1) Among breastfeeding women and their infants, *was the use of POCs* associated with a difference in breastfeeding or infant outcomes, compared with nonuse of POCs? (2) Among breastfeeding women and their infants, *was initiation of POCs before 6 weeks postpartum* associated with a difference in breastfeeding or infant outcomes, compared initiation of POCs at 6 weeks or later?

2.2. Search strategy

We searched PubMed for relevant articles in all languages published or in press from database inception through December 15, 2014 (see Appendix I). We searched reference lists of relevant articles for additional citations of interest. We did not consider unpublished studies, abstracts or dissertations. We had previously contacted one author for clarification regarding allocation between treatment groups [15] and contacted another for clarification of method of analysis and measures of association of interest [16].

2.3. Study selection

We included primary reports of studies of breastfeeding women who received POCs (oral, injectable, implantable or hormonal IUDs), as well as progesterone pellets. Studies assessing progesterone vaginal rings (PVRs) [17] were excluded as they were reviewed separately [18]. The main outcomes were breastfeeding performance and infant health. Studies that reported solely on self-perceived ability to breastfeed (without any reporting on duration of breastfeeding), breastfeeding episodes, milk composition or milk quantity were excluded. Studies that did not specify when contraceptives were initiated were also excluded. Studies that compared use of POCs with use of another type of hormonal contraceptive were considered indirect evidence. We included trials, cohort and case–control studies and excluded cross-sectional and noncomparative studies.

2.4. Study quality assessment

Two authors assessed the quality of each study (SP and NT) using the United States Preventive Services Task Force evidence grading system [19].

2.5. Data synthesis

We used a standard data abstraction template to systematically assess and summarize the evidence. Because many studies and recommendations separate results by the use of contraception before and after 6 weeks postpartum, we structured this report similarly. Summary odds ratios were not calculated, given the heterogeneity of interventions, results and nonquantifiable outcomes reported.

3. Results

The literature search yielded 848 articles; 771 were excluded on title and abstract review and 28 were excluded after full-text review, leaving 49 reports meeting inclusion criteria. Since this review was last updated in 2008 [13], four new randomized controlled trials (RCTs) [20–23] and five new observational studies were published [16,24–27], and an additional

five observational studies that were not included in the 2008 review were identified [28–32], for a total of eight reports of RCTs and 41 reports of nonrandomized clinical trials or observational studies for review (Table 1). These 49 articles reported on 47 different studies investigating the use of POCs in breastfeeding women and reported clinically relevant outcomes of infant growth, health or breastfeeding performance.

Results for Key Question One, then for Key Question Two, are presented by study design and by time of contraceptive initiation: less than 6 weeks or greater than or equal to 6 weeks postpartum. Newly identified studies are presented first, followed by a brief summary of findings from the previous review. Nonrandomized clinical trials are presented together with observational data.

3.1. Key Question One, initiation at less than 6 weeks postpartum: Lactation performance

3.1.1. Randomized clinical trials—Four RCTs [21,33–35] investigated POC initiation within 6 weeks postpartum. A new RCT provides indirect evidence: this trial randomized 127 women planning to breastfeed to either POPs or combined oral contraceptives (COCs), started 2 weeks postpartum [21]. No difference was noted between groups in breastfeeding continuation or supplementation over 6 months.

Three RCTs were included in the previous review. In one, fewer levonorgestrel (LNG) IUD users were breastfeeding than copper (Cu) IUD users at 75 days; this difference disappeared at 6 months [34]. Mean duration of breastfeeding was similar. Another investigating the use of norethindrone compared with placebo found no difference between groups in breastfeeding initiation [33]. A third found no difference in breastfeeding outcomes over 12 weeks between women who received injectable norethisterone enanthate (NET-EN) or placebo [35].

3.1.2. Nonrandomized clinical trials and observational studies

3.1.2.1. Injectables.: In 11 nonrandomized clinical trials and observational studies, four of which are newly included since the last review [16,25,27,31], progestogen-only injectables (POIs) (either DMPA or NET-EN) were initiated in the first 6 weeks postpartum; most of these found either no effect on breastfeeding outcomes or improved outcomes among DMPA users. In one new prospective cohort study, women initiated DMPA or a nonhormonal method postpartum; no difference in breastfeeding frequency or continuation was observed at 6 weeks or at 3 or 6 months [27]. A second prospective cohort study found that women who initiated DMPA after 72 h were more likely to exclusively breastfeed at 3 months than those who either did not initiate or initiated early [16]. No differences emerged in exclusive breastfeeding to 6 months for those who did not initiate DMPA compared with those who initiated by 3 or 6 months. A third retrospective cohort study found no significant differences in duration or continuation of breastfeeding through 6 weeks between women who initiated DMPA before 5 days postpartum compared with those who did not [25]. The fourth new study prospectively investigated the use of DMPA compared with use of other contraceptive methods [31]. Most of the women studied received DMPA within the first 3 months postpartum. Those who received DMPA were more likely to be fully breastfeeding at 3 and 6 months postpartum and were more likely to continue breastfeeding through

12 and 18 months. Of women who received DMPA in the first 3 months, 35% were still breastfeeding at 12 months compared with 67% of those who received DMPA after 3 months.

The remaining studies were included previously. One found that no women using NET-EN, DMPA or nonhormonal methods supplemented breastfeeding in the 6-month study period [36]. Another found that women using DMPA breastfed for longer than a historical control group, although no difference was noted compared with IUD users [37]. Two other studies similarly found longer duration of breastfeeding among women using DMPA compared with nonhormonal methods [38,39]. Another found that NET-EN and (presumably nonhormonal) IUD users had no difference in time to first supplementary feeding, but infants of IUD users weaned earlier [40]. Mothers who received either DMPA or a nonhormonal method at hospital discharge had no differences in breastfeeding exclusivity, supplementation or duration [41]. Finally, when DMPA initiated at hospital discharge was compared with nonhormonal method use, no differences were found in breastfeeding at 2 or 6 weeks, although fewer DMPA users were breastfeeding at 4 weeks [42].

3.1.2.2. POPs.: Eight observational studies assessed the use of POPs in the first 6 weeks postpartum; all were included in the previous review and found either no differences between POP users and nonusers or improved breastfeeding outcomes with POP use. In a nonrandomized trial, POP users initiated breastfeeding earlier than placebo users [43]. Other studies found no difference in breastfeeding duration for POP users compared with historical controls [37] or compared with nonhormonal users [39,44], while two found longer breastfeeding duration among POP users compared with historical controls [45] or IUD users [46]. Finally, two studies found less supplementation among POP users than nonhormonal users [47,48].

3.1.2.3. Implants.: Five observational studies, all in the previous review, largely found no difference in outcomes when assessing the impact of implants in the first 6 weeks postpartum. Women using a norethindrone implant were more likely to supplement breastfeeding at 3 months than those using condoms, but no differences were noted at any other time through 6 months or in the mean duration of breastfeeding [49]. Two studies found no difference in supplementation comparing LNG implant with IUD users [40,50]; one of these also found no difference in breastfeeding duration [50]. Users of nomegestrol implants compared with IUD users similarly had no difference in time of weaning or breastfeeding rates through 12 months [51]. Finally, breastfeeding duration did not differ between users of an etonogestrel (ETG) implant compared with Cu-IUD users over 3 years [52,53].

3.1.2.4. Multiple POCs.: One study, included previously, assessed users of the LNG implant or POPs (analyzed together) and found no differences in breastfeeding initiation or exclusivity, although POC users were less likely to be breastfeeding than nonhormonal users at one of three time points [42].

3.1.2.5. Nonorally available progestogens.: Progesterone, unlike progestogens, is not absorbable orally; therefore, use during breastfeeding is believed to be safe for a neonate. As

it is absorbed by the mother, it could impact breastfeeding. Two studies examined the use of progesterone pellets in the first 6 weeks postpartum; both were included in the previous review. Neither showed an impact on continuation of breastfeeding at 6 months [54] or at 6 and 12 months [55], compared with Cu-IUD use.

3.2. Initiation at ≥6 weeks postpartum: Lactation performance

One RCT and 13 observational studies (four newly identified [24,26,28,30]) evaluated the use of POCs initiated 6 weeks postpartum or more. None of these reported negative impacts on breastfeeding outcomes among POC users compared with nonusers, with the exception of one observational study that found that the average age of supplementation was younger among POP users compared with IUD users [30].

3.2.1. RCTs—One RCT, previously reviewed, found no difference between Cu-IUD and LNG-IUD users in duration of breastfeeding or supplementation at 6–8 weeks postpartum [56].

3.2.2. Observational studies

3.2.2.1. Injectables.: Three observational studies (one new) were identified. The new study did not find supplementation among infants of mothers receiving injectables nor among those who received no method [36]. Among the studies included in the previous review, one found no difference between DMPA and nonhormonal users in breastfeeding discontinuation or initiation of complementary foods [57]. Another found no difference in breastfeeding duration within study sites between DMPA and NET-EN users, compared with nonhormonal method users, although differences were seen between sites [58,59].

3.2.2.2. POPs.: Four studies (one new) assessed the impact of POPs on breastfeeding outcomes. In the new study, a nonrandomized trial [30], women used POPs, a Cu-IUD plus placebo pill or one of several combined hormonal methods. The average age of supplementation was lower in the POP group compared with the IUD group (11.2 vs. 15 weeks), although statistical comparisons were not reported. Among the studies included in the prior review, one found no difference in complementary feeding or breastfeeding continuation up to 24 weeks when comparing POP users with nonhormonal users [57]. Two others found no difference in breastfeeding duration between POP and nonhormonal users [58–60].

3.2.2.3. Implants and hormonal IUDs.: Six studies, two of which are new, assessed the impact of implant or hormonal IUD use on breastfeeding outcomes; none found differences between groups. One new study assessed the effect of both the ETG implant and the LNG-IUD compared with Cu-IUD and found no differences between groups in mean duration of breastfeeding at 6 months [24]. The other new study included LNG implant and Cu-IUD users and found no difference in the percentage of fully breastfeeding at month 6 or 12 and no difference in breastfeeding duration [28].

In one of the previously reviewed studies, women who received a norethindrone implant were similar to condom users in supplementation and breastfeeding continuation to 8

months [49]. In three studies of women who initiated the LNG implant, similar duration of breastfeeding was seen among both hormonal and nonhormonal users [58–62].

3.2.2.4. Multiple progestogen-only methods.: One new study assessed the impact of multiple POCs without presenting outcomes separately by method. This prospective cohort found no difference in duration of breastfeeding between users of POCs and nonhormonal methods over 6 months [26].

3.2.2.5. Nonorally available progestogens.: Three studies, none new, assessed the impact of nonorally available progestogens (progesterone pellets and nesterone or elcometrine implants) on breastfeeding outcomes. In two of these, breastfeeding duration was similar between women using progesterone pellets [54] or a nesterone implant [63], compared with Cu-IUD. Elcometrine implant users had a higher rate of breastfeeding at 3 and 6 months and similar rates at 9–12 months compared with Cu-IUD users [64].

3.3. Initiation less than 6 weeks postpartum: Infant outcomes

Thirty-seven studies (four RCTs, 32 observational studies and one cohort study with a nested RCT) were identified, including many of the studies previously described. Although some studies found differences in growth, health or development at some individual time points, most demonstrated no adverse impact of POCs.

3.3.1. RCTs—Three trials were identified. One of these studies is new and provides indirect evidence; the other two were included in the previous review. In the new study, women initiated either POPs or COCs at 2 weeks postpartum; no differences emerged in infant weight, length or head circumference through 8 weeks [21]. In a study of POPs or placebo, no differences were reported for infant weight gain at 14 days [33]. Similarly, infants of LNG-IUD users had similar weight, height and health through 12 months compared with Cu-IUD users [34].

3.3.2. Observational studies

3.3.2.1. Injectables.: Seven observational studies, three newly identified [27,29,32], assessed infant outcomes after initiation of POIs; all either found no detrimental effect or a protective effect of injectables on infant growth and health. A new cohort study of 250 women found no differences in infant growth or reports of illness up to 6 months when comparing users of DMPA initiated within 10 days postpartum with users of nonhormonal methods [27]. Another newly identified cohort study found no difference in infant weight gain up to 46 months between infants whose mothers had been exposed to DMPA at various time points and those who did not receive DMPA prior to 9 months postpartum [32]. No significant differences were found between groups in infant infections, although a subgroup that received DMPA within 2 days postpartum had a 75% higher incidence than the other groups (statistics not reported). Another cohort study included infants who were exposed to DMPA during breastfeeding (but not during their mother’s pregnancy), during both pregnancy and breastfeeding or not at all [29]. Infants who were exposed only during breastfeeding were no more likely than the unexposed to have a height or weight over two standard deviations below the mean. Infants exposed to DMPA during breastfeeding

(including those exposed during pregnancy) were more likely to have short stature; this difference was no longer significant after adjusting for socioeconomic factors and no effect on weight was seen. Follow-up period was unspecified.

The remaining four studies were included in the previous review. In one, infant weight gain was the same for NET-EN, DMPA and Cu-IUD users up to month 3, after which weight gain was greater in both the DMPA and NET-EN groups [36]. No physical, mental or radiological differences were seen through 18 months. Another study found no effect of maternal DMPA use on infant weight, development or health compared with nonhormonal method use through 3–6 years of follow-up [38]. One child death was reported in the nonhormonal group, and none was reported in the DMPA group. In another study, infants had no adverse effects with maternal NET-EN use through 30 months of age when compared with nonhormonal method use; specific outcomes were not provided [39]. The fourth study found no difference in growth or development among infants of NET-EN users compared with infants of Cu-IUD users over 12 months [40].

3.3.2.2. POPs.: Six observational studies or nonrandomized trials, none new in this review, assessed infant outcomes associated with POP use; most found no adverse effects. In one study, infants of women using POPs had greater weight increase than placebo users at day 14 [43]. Another study found no difference in urinary FSH, LH or testosterone among male infants of POP users compared with users of no method at 4 weeks [65]. Another study found no adverse effects of POPs up to an average of 4.5 years of age, compared with infants of women who used the lactational amenorrhea method (LAM) or the IUD (presumably nonhormonal) [39]. Two studies found no growth differences between infants of mothers using POPs compared with nonhormonal users [47,48]; one of these also found no difference in hospitalizations [47], while the other found more frequent minor illnesses and greater mortality (3 vs. 0 deaths) among children of mothers who used nonhormonal methods [48]. Finally, infants of desogestrel users had temporary breast enlargement (2 infants) and perceived increased sweating (1 infant), compared with no adverse effects among infants of Cu-IUD users [46]. Follow-up through 2.5 years revealed no clinically relevant effects of desogestrel on the growth or health of the infants.

3.3.2.3. Implants.: Eight studies that assessed the impact of implants were included, none of which is new; generally no adverse effects were reported. In one study, infant weight was no different between norethindrone implant and barrier method users [49]. Another found no health or serum immunoglobulin differences between infants of LNG implant and nonhormonal users [66] and another found no differences in mean FSH, LH or testosterone [65]. One study found slower weight gain in infants of LNG implant users up to 3 months, compared with Cu-IUD users. This difference disappeared at 4–6 months; however, length increased less among infants of LNG users compared with Cu-IUD users [50]. No differences in morbidity were reported. In another study, infant lengths did not differ and weight was greater among infants of LNG implant users [67], and in a third, no differences were found between implant users and nonhormonal users in growth or development [40]. A study of the nomegestrol implant compared with Cu-IUD found no difference in growth or health; greater infant mortality was seen in the implant group

(six deaths from gastroenteritis, seizures and pneumonia, compared with one death from gastroenteritis in the Cu-IUD group) but was not statistically significant [51]. Finally, a study of ETG implants compared with the Cu-IUD found no differences in infant growth, adverse events, respiratory or skin disorders or developmental scores [52,53].

3.3.2.4. Nonorally available progestogens.: Two studies reported no difference in infant growth or health comparing progesterone pellet users with placebo or Cu-IUD users [54,55].

3.4. Initiation at ≥6 weeks: Infant outcomes

Most of the studies described above also reported on infant outcomes. The majority found no significant differences between infants of POC users and nonhormonal method users, although differences in both directions were noted in some comparisons.

3.4.1. RCTs—Two RCTs (neither new) investigated the effect of POC initiation after 6 weeks postpartum. In both, no differences in infant growth or development were seen between users of the LNG-IUD compared with the Cu-IUD through 1 year [56] or between users of POPs or DMPA compared with nonhormonal method users through 24 weeks [57].

3.4.2. Observational studies

3.4.2.1. Injectables.: Three observational studies (none new) assessed the impact of maternal use of POIs initiated at 6 weeks postpartum or later; none is new. One found increased weight gain among infants of DMPA and NET-EN users compared with nonhormonal users and also found no physical, mental or radiological differences over 18 months [36]. Another similarly found no difference in mean weight between DMPA users and nonhormonal users through 24 months [57]. Another study showed more weight gain among infants of DMPA and NET-EN users at some time points (3 and 12 months) and no difference at others (6 and 9 months). The majority of comparisons in developmental tests were similar, although some tests favored nonhormonal methods and others favored DMPA or NET-EN [58,59].

3.4.2.2. POPs.: Four studies, one new [30], assessed the impact of POPs. The new study found no difference in infant growth between those whose mothers used a POP compared with those whose mothers used an IUD plus placebo pill up to 32 weeks [30]. In the other three studies, one found smaller increase in arm circumference at two sites among infants of POP users compared with nonhormonal users but found no difference for other growth measures or for the majority of developmental test results [58,59]. The second found no differences in infant weight gain over 6 months when comparing infants of POC users with those of users of multiple other hormonal and nonhormonal methods [60]. The third found no difference in infant growth (length, weight, arm circumference) among infants of women using POPs compared with those using nonhormonal methods [57]

3.4.2.3. Implants/hormonal IUDs.: Six studies, two new [24,28], assessed infants whose mothers initiated progestogen-only implants or hormonal IUDs. In one new study, women initiated the ETG implant or LNG-IUD 6 weeks postpartum; no difference was found in infant weight or height through 6 months, although infants in the implant group had

less increase in tibial length than infants in the Cu-IUD group [24]. The other found no differences over 12 months in infant weight between users of the implant and users of the Cu-IUD initiated at 8 weeks [28].

The remaining four studies were included previously. In one, infants of women who used a norethindrone implant had no differences in weight gain compared with those who used nonhormonal implants [49]. Likewise infants of LNG implant users had similar growth and development compared with nonhormonal users, although a few differences were noted in some of the multiple developmental tests [58,59]. In two studies of LNG implant use compared with nonhormonal methods, no differences were noted between groups in infant weight gain [60,62], although in one of the studies, a higher incidence of respiratory infections and skin conditions was noted among infants whose mothers used an LNG implant [62]; more urologic and neurological conditions occurred among infants of Cu-IUD users.

3.4.2.4. Multiple progestogen-only methods.: One study (not new) included infants of mothers using various POCs and found that infant growth was generally the same between POC and nonhormonal users [68].

3.4.2.5. Nonorally available progestogens.: Three studies reported on infant outcomes of mothers using nonorally available progestogens, none new. Infant growth was no different in users of nesterone pellets compared with nonhormonal methods [63]; neither infant growth nor health was different between users of progesterone pellets and users of nonhormonal methods [54]. Similarly, there was no difference in infant growth or development between infants of users of nesterone implants and Cu-IUD users [64].

3.5. Key Question Two: Early versus delayed initiation

In total, eight studies address the effect of initiation of POCs before 6 weeks postpartum compared with later initiation, of which five are new [16,20,22,23,32]. The majority found no effect on breastfeeding or infant outcomes, although one RCT found that more women continued breastfeeding at 6 months in the later initiation group [22] and another found more infections in infants of DMPA users [32].

3.5.1. Breastfeeding outcomes: RCTs and observational studies—Six of the studies assessed breastfeeding outcomes when POCs were initiated early or late postpartum (three RCTs, three observational). All three RCTs and one of the observational studies are new. One RCT compared women using ETG implants immediately postpartum versus DMPA initiated at 6 weeks [20]. No differences were seen between groups in the percentage of women exclusively breastfeeding at 6 or 12 weeks. Another RCT compared postplacental placement of LNG-IUD with delayed placement at 6–8 weeks and found no difference in breastfeeding initiation between groups or in breastfeeding continuation at 6–8 weeks; women in the delayed group were more likely to be breastfeeding at 6 months [22]. A final study compared women randomly assigned to the ETG implant either 1–3 days postpartum or at 4–8 weeks postpartum and found no significant difference in breastfeeding outcomes [23].

One new observational study found that women who initiated DMPA after 72 h postpartum were more likely to be breastfeeding at 3 months than those who initiated before 72 h or who did not use DMPA [16]. In the other observational studies, norethindrone implant initiated early compared with delayed was not associated with differences in supplementary feeding or continuation of breastfeeding [49], and women who initiated progesterone pellets later were more likely to be supplementing breastfeeding than those who initiated early [54].

3.5.2. Infant outcomes: Observational studies—No RCTs and four observational studies (one new [32]) were identified for infant outcomes. The new study found that women who received DMPA within 48 h postpartum reported a higher incidence of infectious diseases in their infants than those who initiated DMPA later or not at all [32].

Among previously included studies, early versus delayed DMPA or NET-EN was not associated with any differences in growth, development or health [36], nor was early versus delayed norethindrone associated with growth differences [49]. Use of progesterone pellets was not associated with any differences in growth, development or health [54].

4. Discussion

Overall, evidence from 49 articles reporting on 47 studies on use of POCs during breastfeeding is of poor to fair methodological quality. Of the 14 studies that were newly included in this review, four were older studies [29–32] of poor quality and one was published in 1999 and of fair quality [28]. None of these older studies showed any negative effect of use of POCs on breastfeeding or infant outcomes. Of the nine studies that were published since the last review, four were RCTs. One of the four trials suggested that early, compared with delayed, postpartum initiation of the LNG-IUD was associated with shorter breastfeeding duration and less breastfeeding exclusivity at 6 months [22]. However, two other RCTs found no differences [20,23]. The fourth new trial provides indirect evidence demonstrating no difference in outcomes between POPs compared with COCs [21]. Among the newly identified observational studies, findings were generally consistent with the observational studies in the previous review, with no adverse effects noted on breastfeeding or infant outcomes.

Exogenous administration of POCs could theoretically inhibit breastfeeding [69]; however, the evidence in this review does not generally support a negative impact on breastfeeding outcomes. Studies examining the initiation of POCs among postpartum women overall demonstrated no adverse effects on measures of breastfeeding success, such as duration of breastfeeding or time to supplementation, although a few reported differences in both positive and negative directions at individual time points. The preponderance of the evidence points toward no deleterious impact of POCs on breastfeeding success, although further study is warranted to examine the impact of immediate postpartum placement of the LNG-IUD.

Theoretical concerns also have been raised regarding the impact of exposure to progestogens on neonates, particularly in the first 6 weeks of life [7]. Studies identified in this review showed no consistent adverse effects of exposure to progestogens through breast milk on

infant health outcomes such as growth, development and health through the first few years of life. We identified no data to inform a conclusion on longer-term effects and any such effects remain unknown.

The PVR was not addressed in this review. A recent review concluded that PVR use among breastfeeding women did not affect breastfeeding performance or infant growth during the first year postpartum [18].

Our ability to draw firm conclusions is limited as most studies are observational, have lacked clear definitions of breastfeeding patterns and failed to control for potential confounders [70]. Many did not provide information key to determining their quality and did not perform tests of significance. Some were not informative to our cutoff point of 6 weeks as participants initiated both before 6 weeks and after. Initiation before 6 weeks ranged from immediately postpartum to nearly 42 days.

In 2014, the WHO Expert Working Group reviewed this evidence to evaluate medical eligibility criteria for the use of POCs among breastfeeding women. All of the abovementioned studies were reviewed with the exception of one, which was identified after the meeting and found no deleterious effects of POCs [27]. The findings of this systematic review were incorporated into the recent update of the MEC [71].

5. Conclusion

Consistent evidence by multiple measures of successful breastfeeding, largely from fair or poor quality observational studies, suggests that POCs, when used by lactating women, do not compromise a woman's ability to breastfeed. Evidence that POCs do not adversely affect infant growth, health or development during the first year postpartum is generally consistent across observational and randomized studies. Further research is necessary to determine any effects on child health or development beyond the first year. Evidence newly added to this review is largely consistent with the previous evidence.

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Appendix I

(((((((progesterone [mesh]) OR progestogen [tw]) OR progesterone [tw]) OR progestogen [tw])) OR ((((((((((progestational hormones [mesh]) OR progestogen [tw])) AND contracept*)) AND (((((oral [tw]) OR pill [tw]) OR pills [tw]) OR tablet [tw]) OR tablets [tw])))) OR ((((((((((dmpa [tw]) OR medroxyprogesterone 17-acetate) OR net en [tw]) OR norethisterone-enanthate [tw]) OR depot medroxyprogesterone [tw]) OR depo medroxyprogesterone [tw]) OR depotmedroxyprogesterone [tw]) OR depomedroxyprogesterone [tw])) AND ((contracept*) OR inject*))) OR ((implant*) AND ((((((((((norplant [tw]) OR uniplant [tw]) OR jadelle [tw]) OR implanon [tw]) OR nexplanon [tw]) OR sino [tw]) OR simplant [tw]) OR sino-implant [tw]) OR levonorgestrel [tw])

OR etonogestrel [tw])) OR ((mirena [tw]) OR ((levonorgestrel [tw]) AND (((((((iud [tw]) OR intra uterine [tw]) OR intra-uterine [tw]) OR intrauterine devices [mesh])))))))) AND (((((breast feeding [mesh]) OR breast feeding [tw]) OR breastfeeding [tw]) OR lactation [mesh]) OR lactation [tw])

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Table 1

Included studies

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
Kamal, 1969 [30] Not stated *Newly identified*	Nonrandomized clinical trial Egypt *N*=120 PP women (data available on 50)	6–10 weeks PP: POP (0.5 mg lynestrenol) IUD+placebo 2 kinds of COCs, 1 combined injectable contraceptive (not reported here) Allocation not reported	BF performance (age of supplementation) Infant growth (growth curve, percent weight increase) Follow-up 32 weeks	BF outcomes –Average age of supplementation 11.2 weeks POP group, 15 weeks placebo (statistics not reported) Infant outcomes –No relation between growth curve and method used	Strengths –Double blinded Weaknesses –No statistical analysis reported for comparisons of interest –High, but not clearly reported, loss to follow-up –Number of participants/group not reported	Level II-1 Poor Key Question 1
Kamal, 1970 [43] Not stated	Nonrandomized clinical trial Egypt *N*=40 primiparous and multiparous women, ages 20–37 years	2 days PP: 10=placebo 10=POP (lynestrenol 500 mcg) 10=COC (results not presented) 10=ethinyl estradiol (results not presented)	BF performance (initiation of lactation) Infant growth (weight) Follow-up 14 days	BF outcomes –Lactation initiation earlier (3 vs. 5 days) in POP than placebo group Infant outcomes –Greatest weight increase in POP-exposed infants	Strengths: –Included primiparas Weaknesses: –Nonrandomized –Small sample size –Short follow-up –No statistical comparisons	Level II-1 Poor Key Question 1
Karim, 1971 [36] Not stated	Prospective cohort Egypt *N*=331 women after normal delivery	7 days PP: 68=NET-EN (200 mg) 51=DMPA (150 mg) 100=NH 42 days PP: 57=NET-EN 55=DMPA	BF performance (supplementation) Infant growth and health (weight, physical exam, dentition, mentality, walking, radiographs) Follow-up 18 months	BF outcomes –No BF supplementation reported up to 6 months in any groups Infant outcomes –After 3rd month, infant weight gain per month higher in all POC groups than in NH controls; weight gain in hormonal groups equivalent –No physical, mental or radiologic differences in infants between groups	Weaknesses: –Percent follow- up of infants not reported –No standardized techniques to measure health and specifics of health outcomes not reported	Level II-2, Poor Key Questions 1 and 2
Guiloff et al., 1974 [37] Population council, Warner-Lambert Research Institute	Cohort Chile *N*=696 multiparous women, ages 16–40 years Historical control was composed of the past lactation history of a subset of women enrolled in the study who were still BF at 30 days	1–2 days PP: 80=DMPA (250 mg im q 6 months) 30 days PP: 33=DMPA 54=Chlormadione acetate (250 mg im q 3 months) 81=Quingestanol acetate (300 mcg) 81=IUD Other participants	BF performance (mean duration of lactation) Follow-up 12 months	BF outcomes *Mean lactation duration (presented as mean months with 95% CI)* DMPA 1–2 days PP: 6.7 (5.2–8.7) Historical control: 4.8 (4.1–5.3) DMPA 30 days PP: 9.3 (6.0–10.0) Chlormadione acetate 30 days PP: 7.5 months (4.7–9.7) Quingestanol acetate 30 days PP: 4.2 (2.8–5.6) IUD 30 days PP: 7.7 (6.8–8.9) Historical control: 5.3 (4.8–5.8)	Weaknesses: –Unclear if prospective or retrospective –Historical control –Historical recollection of duration of lactation	Level II-2 Poor Key Question 1

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
		used COCs (results not reported here)				
Giner-Velasquez et al., 1976 [33] Not stated	RCT Mexico *N*=20 healthy women, ages 18–36 years	≤14 h PP: 12=NET (350 mcg) 8=Placebo	BF performance (initiation) Infant growth (weight) Follow-up 14 days	BF outcomes No difference between groups in BF initiation (statistics not reported) Infant outcomes No difference between groups in weight gain (average 493 g placebo, 441 g NET, difference not significant)	Weaknesses: –Methods poorly described –Small sample size –Follow-up and exclusions not described	Level I, Poor Key Question 1
Zanartu et al., 1976 [31] CEBRE, University of Chile Medical School *Newly identified*	Prospective cohort *N*=406 fully BF women using DMPA with at least 18 months follow-up, 173 controls	First 30 days PP: *N*=133 DMPA 30–90 days PP: *N*=206 DMPA 30–90 days PP 91–180 days PP: *N*=67 DMPA (DMPA 150 or 250–300 mg) *N*=173 no DMPA (and either received education about BF or no intervention)	BF performance (exclusive and partial lactation status at 3, 6, 12, 18 months) Follow-up 18 months	BF outcomes 3rd month/6th month PP: 94%/80% DMPA group fully BF; fewer in non-DMPA group (p<.001) 12th/18th month PP: 42%/10% still BF; fewer in non-DMPA group (p<.001) Of those who received DMPA up to 90 days PP, 35% still BF at 12 months (vs. 64% who received after 90 days, no statistics)	Strengths: –High percentage with follow-up (406/500 with at least 18 months follow-up) Weaknesses: –Unclear if non-DMPA users were using other hormonal or NH contraceptives –No separate analysis by DMPA dose; minimal analysis by timing; no statistical analysis for indirect comparison –Wide range in timing of DMPA administration –No statistical analyses	Level II-2, Poor Key Question 1
Zanartu et al., 1976 [45] Ayerst	Nonrandomized clinical trial Chile *N*=100 healthy women, ages 19–42 years	3rd to 10th week PP: 100=Chlormadione acetate 0.6 mg 173=NH(historical control; some inert IUD, some no method)	BF performance (duration) Follow-up 18 months	BF outcomes *At 3 months:* 98% Chlormadione still BF 76% NH still BF *At 6 months:* 80% (POP) and 56% (NH) still BF *At 12 months:* 42% (POP) and 0% (NH) still BF (p<.001)	Weaknesses: –Historical control –Wide variation in timing of contraceptive initiation –Loss to follow-up not reported –Statistical analyses not reported for all outcomes of interest	Level II-1, Poor Key Question 1
Seth et al., 1977 [49] WHO	Cohort India *N*=50 healthy, women, ages 20–40 years	6 days PP: 23=Implant (40 mg norethindrone acetate) (early) 6 weeks PP: 12=Implant (delayed) 15=NH (Condoms/gel)	BF performance (continued BF at 8 months, supplementation rates) Infant growth (weight) Follow-up 11 months	BF outcomes *Still BF at 8 months* 80% NH, 56.6% early, 66.6% delayed, difference not significant *3 months supplementation* Early implant 56.4%, controls 40% (p<.05), other times, NS Infant outcomes No differences between groups in weight	Weaknesses: –Small sample size –Methods poorly described –Baseline characteristics not described –Percent follow-up not reported	Level II-2, Poor Key Questions 1 and 2

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
Croxatto et al., 1982 [55] Population Council and Canadian International Development Research Center	Cohort Chile *N*=439 healthy women who did not hold jobs, ages 18–35 years	30–35 days PP: 84=Progesterone pellets (100 mg) 130=Placebo injectable 125=Cu T200 IUD	BF performance (fully, partially or not BF at follow-up visits) Infant growth (weight) Infant health (reports of intercurrent illness) Follow-up 12 months	BF outcomes *Fully BF*: No significant difference between groups at 3, 6 or 9 months *BF at 6 months* 51.2% progesterone 58.3% IUD *BF at 12 months* 10.7% progesterone 17.6% IUD (p<.05) Infant outcomes No differences in infant weight gain among groups (4515 g progesterone, 4633 placebo, 4801 IUD, not statistically significant) or health (no statistics reported)	Weaknesses: –Little description of intercurrent illnesses (or their assessment) –High rates of discontinuation/termination from study/loss to follow-up in all groups	Level II-2, Fair Key Question 1
Dahlberg, 1982 [32] No funding *Newly identified*	Retrospective cohort Thailand *N*=331 infants born at Thai hospital between 1977 and 1979	Some time in 1st 9 months PP: 210=Some exposure to DMPA 121=No exposure to DMPA	Infant growth (weight) Infant health (incidence of infectious diseases leading to clinic visits) Follow-up up to 46 months	Infant outcomes *Weight gain* No difference between groups at any time point in follow-up, regardless of length of exposure *Health* No difference in average numbers of infectious diseases reported per year between groups (although subgroup who received DMPA at 2 days PP had 75% higher incidence than other groups, statistics not reported)	Strengths: –Subgroup data presented with different amounts of DMPA exposure Weaknesses: –Data obtained solely through record review –Statistical analysis not reported –Analytical methods not clearly described –Timing of exposure to DMPA not clear –Wide variation in when DMPA was given PP	Level II-2, Poor Key Questions 1 and 2
Heikkila and Luukkainen, 1982 [34] Population Council, US Agency for International Development, Ford Foundation	RCT (with change to protocol partway through trial) Finland *N*=110 women	32–56 days PP: 30=LNG (10 mcg/day IUD) 40=LNG (30 mcg/day IUD) 40=Copper IUD	BF performance (duration, time to supplementation) Infant growth (height, weight) Infant development (time of walking, tooth eruption) Infant health (infectious diseases) Follow-up 12 months	BF outcomes *BF continuation 75 days postinsertion*: 79% in IUD group, 56% LNG 30 group, p<.05 (results for LNG-10 not reported) *BF continuation 6 months postinsertion*: no difference among 3 groups *Median duration of BF* 141 days LNG-10; 154 days LNG-30; 197 days Cu-IUD (difference significant) *Mean duration*: no significant difference *Supplementation*: no significant difference Infant outcomes *Growth and development* No differences in height, weight, time of walking, tooth eruption *Health* No differences between groups in respiratory/middle ear infections	Weaknesses: –Allocation concealment and randomization sequence ill-described –Mid-way through trial, added lower-dose IUD and changed allocation scheme –Copper IUD group younger and less parous –Illnesses not recorded or assessed systematically	Level I, Poor Key Question 1
West et al., 1983 [44]	Cohort Scotland *N*= 227 healthy	Up to 8 weeks PP: 84=Norethisterone 0.35 mg	BF performance (duration, supplementation)	BF outcomes: At 3 months: 62% POP, 62% NH still BF	Weaknesses –Follow-up by postal survey	Level II-2, Poor

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
Medical Research Council	women, fully BF (data available on 203)	(76% by week 4) 29=COC 89=NH		At 5 months: 51% POP, 53% NH still BF (statistics not reported)	–No statistical analysis –Unclear when methods were initiated	Key Question 1
Diaz et al., 1984 [54] Instituto Bioquinico Beta, WHO, International Development Research Centre of Canada, Population Council	Cohort Chile *N*=653 healthy women after normal pregnancy, 18–35 years	30 days PP: 84=Progesterone pellets (100 mg) 125=Cu T200 IUD 130=Placebo injection 60 days PP: 193=Progesterone pellets 121=Cu T200 IUD	BF performance (exclusivity at 6 months and continuation) Infant growth (weight gain at 6 months) and health (how assessed not defined) Follow-up 6 months	BF outcomes: No difference in BF status at 6 months between those initiated at 30 or 60 days PP and their contemporary controls; however, those who initiated at day 60 were more likely to supplement at month 6 than those initiating at day 30 (68% exclusive vs. 53% exclusive, statistics not reported) Infant outcomes *Weight gain* No difference between groups *Health* No negative effects of progesterone on infant health	Strengths –Clear description of methods and analysis Weaknesses: –Women lost to follow-up or discontinuing their method not reported –Statistical analyses not presented for outcomes of interest –No control for confounding –Unclear how infant health was assessed	Level II-2, Poor Key Questions 1 and 2
Jimenez et al., 1984 [38] Upjohn	Retrospective cohort—follow-up to unpublished primary study Chile *N*=270 Women and their children exposed to contraception during lactation, 3–6 years prior	2nd month PP: 128=DMPA (150 mg q 3 months) 142=NH	BF performance (reported duration of lactation) Infant growth (weight, arm circumference, head circumference) Infant health (respiratory infections, diarrheal disease, hospital admissions, mortality) Infant development (standardized physical exam, interview, record review and psychomotor scale)	BF outcomes: Median lactation duration: 21 months DMPA vs. 13 months NH ($p<.05$) Infant outcomes *Growth* No difference between groups in height; weight different between groups but no difference when adjusted for confounders *Health* 1 death in control group (accidental), 0 in DMPA group *Development* No differences between groups in psychomotor development, milestones, health problems, infant height or physical exam	Weaknesses: –Primary study not published –Some outcomes relied on retrospective self-report –Groups dissimilar (mothers in DMPA group older, of higher parity)	Level II-2, Poor Key Question 1
Tankeyoon et al., 1984 [57] WHO	Prospective cohort with nested RCT Hungary Thailand *N*=341 experienced BF women, ages 20–35 years, parity 2–4, after healthy term delivery	6 weeks PP (±3 days): 59=DMPA 111 =NH (barriers, sterilization, IUD) Pill-users (randomized): 85=POP 86=COC (results not reported here)	BF performance (use of complementary food, discontinuation due to perceived inadequate milk supply) Infant growth (weight, length, arm circumference) Follow-up 24 weeks	BF outcomes: No differences in complementary feeding or discontinuation of BF between groups Infant outcomes No differences in mean weight or rate of growth between contraceptive groups	Strengths: –Multicultural and multicenter with nested double blinded RCT Weaknesses: –No power calculation –No details of method switching/discontinuation –No attempt to control analysis for confounders	Level II-2, Poor Key Question 1

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
Abdulla et al., 1985 [66] Rockefeller Foundation	Cohort Egypt *N*=20 healthy women after singleton, term delivery (mean age 29 years)	30–39 days PP: 10=LNG implant 10=Barriers/nothing	Infant health (occurrence of significant illnesses; serum IgA, IgG, IgM) Follow-up 6 months	Infant outcomes No infants had significant illnesses No significant differences between groups in infant serum immunoglobulins	Weaknesses: –Selection and assessment procedures not specified –Small sample size with no power calculations –Percent follow-up not reported	Level II-2, Poor Key Question 1
Shaaban et al., 1985 [50] Rockefeller Foundation	Cohort Egypt *N*=150 healthy, multiparous, BF-experienced women (mean age 29 years) after normal, term delivery	30–42 days PP: 50=LNG implant 50=Cu T380 IUD 50=Barriers/nothing	BF performance (frequency, supplementation) Infant growth (weight, length) Infant health (illness) Follow-up 6 months	BF outcomes No differences in number BF episodes/day or number supplemental feeds Infant outcomes *Growth* Slower weight gain in Norplant group to 3 months (but >50%percentile); no differences at 4–6 months; slower length increase in Norplant group from months 3–6 (but >50% percentile) *Health* No differences in infant morbidity	Weaknesses: –No adjustment of for possible confounders –Differences at baseline between groups –Unclear how infant morbidity was measured	Level II-2, Poor Key Question 1
Shikary et al., 1986 [65] WHO, Population Council	Cohort India *N*=29 women after term delivery of male infants, ages 20–35 years	4 weeks PP: 9=POP (LNG 30 mcg) 10=LNG implant 10=No method	Infant health (daily 4-h urine samples tested for FSH, LH, testosterone) Follow-up 15 weeks	Infant outcomes No significant differences in mean FSH, LH and testosterone area under the curve between the groups	Weaknesses: –Small sample size with no power calculations –Short follow-up	Level II-2, Fair Key Question 1
Zacharias et al., 1986 [39] UpJohn, Ayerst	Prospective cohort Chile *N*=665 women, after term deliveries	3–6 weeks PP: 143=LAM 109=Cu T IUD (presumably NH) 228=DMPA 185 = POP (0.6 mg clogestone acetate)	BF performance (duration) Infant growth and development (not specified) Follow-up of children to a median age of 4.5 years	BF outcomes *Mean duration:* 17 months LAM 21 months IUD 30 DMPA 22 POP (pb.03 for pairwise comparison with DMPA) Infant outcomes *Growth/development* No adverse effects of progestogens (not specified)	Strengths: –Survival analysis techniques Weaknesses: –Measures for growth and development not provided –Statistical comparisons not performed –No attempt to control analysis for confounders –Baseline differences between groups –Infants with “signs of inadequate nutrition” discontinued from study and not reported on	Level II-2, Poor Key Question 1

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
Affandi et al., 1986 [67] Population Council	Cohort Indonesia *N*=120 women after term, healthy delivery, planning to breastfeed ≥6 months	4–6 weeks PP: 60=LNG implant 60=Copper IUD	Infant growth (weight, length) Follow-up 6 months	Infant outcomes Infants in LNG group gained significantly more weight than the IUD group. No differences in length between groups (statistical comparisons, p values not provided)	Weaknesses: –Limited description of statistical analysis and no attempt to control for confounders –Baseline differences between groups –Percent follow-up not reported	Level II-2, Poor Key Question 1
McCann et al., 1989 [47] USAID, Family Health International, Wyeth Pharmaceuticals	Cohort Argentina *N*=500 healthy multiparous women, after term delivery with prior BF experience, ages 30–35 years	1 week PP: 250=LNG (30 mcg) 250=NH methods (54% IUD)	BF performance (continuation, supplementation) Infant growth (weight, length, head circumference, growth velocity) Follow-up 9 months	BF outcomes Median age of initiation of supplementation 5.4 for LNG vs. 4.6 months for NH users (p<.05); also significantly different on survival analysis NH users three times more likely to discontinue BF during study period than LNG users (22 vs. 7, p value not reported) Infant outcomes No differences between groups in infant growth on any measure	Strength: –Survival analysis performed Weaknesses: –Only enrolled older, multiparous women –High loss to follow-up (55% at 9 months) –Statistical analysis not reported on all outcomes of interest –Infant health outcomes collected but not reported	Level II-2, Poor Key Question 1
Moggia et al., 1991 [48] Family Health International	Cohort Argentina *N*=500 healthy women with experience BF, after term delivery, ages 18–35 years (483 in final analysis)	1 week PP: 250=Norgestrel 75 mcg 250=NH methods (75% IUD)	BF performance (supplementation) Infant growth (weight, length, head circumference) Infant health (hospitalizations, minor illnesses, mortality) Follow-up 6 months	BF outcomes: More frequent supplementary feeding in NH group at months 2 and 3 (p<.05), otherwise no difference; no difference in *number* of women supplementing at any time Infant outcomes *Growth* No difference in infant growth *Health* No differences between groups in hospitalizations. Minor illnesses more common in NH group (91 NH, 60 POC, p<.01); 3 infant deaths in NH group, 0 in POP group	Weaknesses: –No primiparous women –Baseline differences between groups (birthweight lower in POP group) –High loss to follow-up (15% POC, 13% NH LTFU over 6 months)	Level II-2, Fair Key Question 1
Shaaban, 1991 [40] WHO, Population Council, Rockefeller Foundation	Cohort Egypt Phase 1: 360 healthy women and their infants Phase 2: PVR and Cu-IUD, results not discussed here	5th to 7th week PP: 120=LNG implant 120=NET-EN injectable 120=IUD	BF performance (age of supplementation, age of weaning) Infant growth (weight, arm circumference, skinfold thickness) Infant development (attainment of milestones) Follow-up 12 months	BF outcomes No differences in timing or type of supplementation IUD users weaned earliest, followed by LNG implant and NET-EN (statistics not reported) Infant outcomes *Growth* No differences in infant growth *Development* No difference in attainment of milestones	Weaknesses: –Methodology poorly described –Baseline characteristics not described –Statistical analyses not reported for outcomes of interest –Percent lost to follow-up not reported	Level II-2, Poor Key Question 1
Pardthaisong, 1992 [29] Ford Foundation	Cohort Thailand *N*=3231 infants	During lactation (any time, 77% initiated between months 1	Infant growth (weight, height) Length of follow-	Infant outcomes *Growth* Relative risk for score below −2Z on growth chart (no exposure	Strengths: –Clear description of methodology	Level II-2, Poor

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
WHO FHI	with varying levels of prenatal and lactational DMPA exposure/ nonexposure	and 3) 857=DMPA only during lactation (not pregnancy) 1215=DMPA du ring lactation, some also during pregnancy 1167=No DMPA	up for lactationally exposed infants unclear	as reference): 1.1 (0.9–1.2) lactational exposure only (no prenatal exposure); 1.2 (1.0–1.3, p<.05) any lactational exposure (including some with prenatal exposure); RR 1.1 (0.9–1.4) for any lactational exposure when adjusted for potential confounders	–Appropriate analytical methods Weaknesses: –Baseline differences noted between DMPA users and nonusers –Unclear length of follow-up –Timing and amount of exposure to DMPA unclear –Unexposed may have been using other hormonal methods	Key Question 1
WHO, 1994 [58,59] WHO	Cohort Egypt, Iran, Thailand, Kenya, Chile, Hungary *N*=2466 married women, after term delivery and their infants	6–8 weeks PP: 475 = POP (LNG or lynestrenol) 541=DMPA 121=NET-EN 453=LNG implant 876=NH (IUD, barriers, sterilization)	BF performance (frequency, duration exclusive BF) Infant growth (weight, arm circumference, skinfold thickness) Infant health (mortality) Infant development (age passed standard developmental test) Follow-up 12 months	BF outcomes: Frequency and duration of BF differed between sites, but not between contraceptive groups within a site *Infant outcomes* *Growth* One site had larger weight increase in NET-EN group (6, 12 months) and DMPA group (3 months) compared to NH group Smaller increase in arm circumference at two sites for POP group (3 months and 3 and 12 months) *Development* 247 comparisons; 32 showed significant differences: in 20, infants in progesterone-only groups passed tests at earlier ages, and in 12, they passed at later ages. *Mortality* No significant differences within sites by method	Strengths: –Large cohort, multicultural and multicenter –Standardized assessment of development –Confounders assessed and controlled for in analysis Weaknesses: –Large differences between sites for BF performance and infant outcomes –Percent lost to follow-up not reported	Level II-2, Fair Key Question 1
Abdel-Aleem et al., 1996 [51] South-to-South Cooperation in Reproductive Health	Cohort Egypt *N*=242 healthy, exclusively BF women and their term infants (mean age 26 years)	2nd PP month: 120=Nomegestrol implant 120=Cu-IUD	BF performance (frequency of BF, % BF at all and exclusively at different time periods) Infant growth (weight, arm circumference, skinfold thickness) Infant health (frequency of diarrhea, fever, cough and mortality) Follow-up 12 months	BF outcomes No significant differences between groups in BF frequency, continuation or exclusivity Infant outcomes *Growth* No differences in infant growth *Health* No significant differences in health. 7 infants died: 6 in implant group (4 gastroenteritis, 1 seizures, 1 pneumonia), 1 (gastroenteritis) in IUD group (not significant, p>.05)	Strengths: –Assessment of infants was blinded to contraceptive group –Power calculations presented Weaknesses: –Underpowered to look at infant health outcomes –Percent follow-up not reported –Baseline differences between groups	Level II-2, Fair Key Question 1
Hannon et al., 1997 [41] National Institutes	Cohort USA *N*=103 women	At the time of hospital discharge:	BF performance (BF continuation and	BF outcomes No difference in duration of lactation (median 10.14 weeks for	Strengths: Sample selection/ methods clearly	Level II-2, Poor

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
of Health and Thomas Wilson Sanitorium	consecutive, term deliveries with ability to follow-up by telephone	45=DMPA 150 mg 52=NH (unspecified)	exclusivity) Follow-up 16 weeks	DMPA vs. 6.57 weeks in NH users, p=.19) No difference in time to supplementation with formula	described Power calculations performed Weaknesses: -Limited duration of follow-up -No infant outcomes -Baseline differences between groups (DMPA younger, unmarried)	Key Question 1
Diaz et al., 1997 [60] WHO, Population council, CONRAD	Cohort with historical control Chile *N*=662 cohabitating parous (1–3) women after term delivery, ages 18–38 years	57±3 days PP: 117=POP (lynestrenol) 187=PVR 120=LNG implant 122=Copper IUD 236=NH (LAM)	BF performance (duration of any and exclusive BF) Infant growth (weight) Follow-up 6 months	BF outcomes No difference between groups for mean and total duration of BF Infant outcomes No differences in growth between groups	Weaknesses: Historical control	Level II-2, Fair Key Question 1
Lawrie et al., 1998 [35] Schering Ltd, Iris Ellen Hodges Trust of the University of the Witwatersrand, South African Medical Research Council, South African Institute for Medical Research	RCT South Africa *N*=166 immediate PP women ages >19 years	<48 h PP: 85=NET-EN 84=Placebo All women additionally used an NH method	BF performance (duration of any BF, exclusive or partial) Maternal depression (not reported here)	BF outcomes No difference between groups in continuation rates at 6 or 12 weeks	Strengths: –Clear description of methods –Enrolled women regardless of past/current BF experience Weaknesses: –Small sample size –BF outcomes were secondary	Level I, Fair Key Question 1
Coutinho et al., 1999 [64] Rockefeller Foundation	Prospective cohort Brazil *N*=135 women, 18–35 years old after term health delivery planning to breastfeed for 6 months and their infants	6 weeks PP: 66=Elcometrine implant 69=Cu-IUD	BF performance (any BF at follow-up time points) Infant growth (weight, arm circumference, skinfold thickness) Infant development (age meeting standard milestones, using developmental tests) Follow-up 12 months	BF outcomes Higher rates in implant group (95–76%) vs. IUD (84–57%) at 3, 6 months (p<.05), no differences at 9, 12 months Infant outcomes *Growth* No differences between groups *Development* No differences in age met developmental milestones	Strengths: –Power calculation performed –Standardized outcomes used and described Weaknesses: –No control for potential confounders	Level II-2, Fair Key Question 1
Diaz et al., 1999 [28]	Prospective cohort	57±3 days PP 29=LNG implant	BF performance (any or exclusive	BF outcomes Fully BF month 6: 93% LNG, 86% IUD (no difference); Fully BF	Strengths: –Clearly described	Level II-2, Fair

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
Population Council *Newly identified*	Chile *N*=108 BF women planning to continue to breastfeed	51=Cu-IUD 28=PVR (results not reported here)	BF up to 6 months, no milk supplementation at 12 months) Infant growth (weight) Follow-up minimum 12 months	month 12: 4% LNG, 10% IUD (no difference) Duration of lactation 15 months LNG, 14 months IUD (no difference) Infant outcomes *Growth* No difference between LNG and Cu-IUD groups at month 1, 6 or 12	methods Weaknesses: –BF/Infant outcomes were secondary –Length of follow-up unclear –Loss to follow-up not specified	Key Question 1
Bjarnadóttir et al., 2001 [46] Organon	Cohort Iceland *N*= 83 multiparous women with prior experience BF, after term delivery, ages 18–40 years	28–56 days PP: 42=Desogestrel 75 mg 41=Cu 375 IUD	BF performance (any BF) Infant growth (length, weight, head circumference) Infant health (intercurrent illness, hospitalizations) Follow-up 2.5 years	BF outcomes: No difference in BF continuation at cycle 4 (5–6 months PP), but at end cycle 7 (8–9 months PP), 78% in desogestrel compared with 59% in IUD group were still BF (statistics not reported) Infant outcomes *Growth* No differences *Health* Temporary breast enlargement in 2 infants, increased sweating in 1 infant in desogestrel group; no occurrences in IUD group. No other differences in health	Strengths: –Power calculations provided –Clearly described methods –Long-term follow-up of exposed infants Weaknesses: –Wide variation in timing of contraceptive initiation	Level II-2, Fair Key Question 1
Baheiraei et al., 2001 [68] Not stated	Prospective cohort Iran *N*=140 women, after healthy term delivery	6 weeks PP: 51=Progestogen-only (DMPA; POP) 89=NH (IUD, condom, sterilization)	Infant growth (weight, length, head circumference) Follow-up 26 weeks	Infant outcomes *Growth* No differences in weight or length at any time; mean head circumference change 1.42 cm (progestogen-only) vs. 1.19 (NH) at 10–13 weeks (pb.05). No differences at other time points	Weaknesses: –Contraceptive use/ switching or formulations are not stated –Separate estimates for different methods not presented –Percent lost to follow-up not reported	Level II-2, Poor Key Question 1
Massai et al., 2001 [63] US Agency for International Development/UN Population Fund	Prospective cohort Chile *N*=200 cohabitating women, after term delivery; ages 18–38 years	55–60 days PP: 100=Nesterone implant 100=Copper IUD	Lactation performance Infant growth (weight gain) Follow-up 1 year	BF outcomes No difference in BF episodes per day or length of BF (273 days implant vs. 263 IUD) Infant outcomes *Growth* No differences	Strengths: –Describes contraceptive switching and discontinuation Weaknesses: –High discontinuation (17% in NES group and 22% in IUD group)	Level II-2, Fair Key Question 1
Halderman and Nelson, 2002 [42] National Institutes of Health	Cohort USA *N*= 3 1 9 women, primarily Hispanic, ages 16–49 years	Prior to discharge from hospital: 102=DMPA 79=LNG implant or POP 138=NH	BF performance (initiation, continuation, supplementation) Follow-up 6 weeks	BF outcomes No difference in BF initiation Any BF at 4 weeks: 83.1% NH, 76.7% POC (p=.022) Any BF at 2, 6 weeks: No difference Exclusivity, supplementation: No difference at any time	Weaknesses: –Short follow-up –No infant outcomes –Aggregate data for methods other than DMPA –Differences between groups at baseline (DMPA younger,	Level II-2, Poor Key Question 1

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
					less parous, less experienced with BF)	
Schiappacasse et al., 2002 [62] (Some data originally reported in Diaz 1985 [61] and as part of WHO 1994 [58,59]) WHO	Prospective cohort from 2 previous studies Chile *N*=442 cohabitating parous (1–3) women after term delivery, ages 18–35 years	55±3 days PP: 220=LNG implant 222=Copper IUD	BF performance (duration) Infant growth (weight, height) and health Follow-up 6 years	BF outcomes No differences in mean and total duration; at 12th month, LNG group had fewer fully BF Infant outcomes *Growth* No differences *Health* Higher incidence of respiratory infection (colds, bronchitis; 44.3 vs. 37.7/100 infant months, p<.0001) and skin conditions (diaper, allergic and bacterial dermatitis, prurigo) in LNG group. Higher incidence of urogenital disease (0.4 vs. 0.2) and psychomotor impairment (23 vs. 12) in IUD group. Hospitalizations greater in LNG group (1% vs. 0.4%, p<.05) among BF infants; but higher in IUD group overall (1.7% vs. 0.6%) Rates for other illnesses similar; 1 death in Norplant group at 7 months for acute diarrhea and septicemia	Strengths –Information on contraceptive switching and discontinuation –Long-term follow-up –Adjusted for potential confounders –Power calculation for infant growth –Blinded assessment of health –Verification with hospital records Weaknesses: –High loss to f/u over time (14% of implant group and 21% of IUD group) –No power calculations for health outcomes –Confounders for skin disease not assessed –Data from infants from different time periods –Pollution levels in Santiago may limit generalizability	Level II-2, Fair Key Question 1
Shaamash et al., 2005 [56] Schering	RCT Egypt *N*=320 women after term delivery	6–8 weeks PP: 163=LNG-IUD 157=Copper IUD	BF performance (duration, number of episodes/day, exclusivity) Infant growth (weight, length, skinfold thickness) and development (age passing standard developmental tests) Follow-up 1 year	BF outcomes No differences in BF duration (149 vs. 160 days for LNG-IUD vs. Cu-IUD) or exclusivity Infant outcomes *Growth* No differences *Development* No differences	Strengths: –Randomized –Adequate allocation concealment –Sample size calculations –Standardized infant development tests Weaknesses: –Enrolment and exclusion criteria not stated –Intent-to-treat analysis and percent loss to follow-up not reported –Infant health	Level I, Fair Key Question 1

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
					outcomes collected but not reported	
Taneepanichskul et al., 2006 [53] Reinprayoon et al., 2000 [52] Organon	Prospective cohort Thailand *N*=80 women after term deliveries, ages 18–40 years	28–56 days PP: 42=ETG implant 38=Copper IUD	BF performance (duration) Infant/child growth (length, weight) and development Infant health (intercurrent illness) Follow-up 3 years	BF outcomes Mean duration of BF: 421 days (Implant) vs. 423 days (IUD), NS Infant outcomes *Growth* No differences between contraceptive groups for length, weight or head circumference *Health* (no statistical comparisons reported) 10/42 implant infants reported skin/appendages disorders vs. 6/38 IUD infants; 17/42 implant infants reported respiratory system disorders vs. 10/38 IUD infants; 3/42 implant infants reported GI disorders vs. 5/38 IUD infants; 2/42 implant infants reported neonatal/infancy disorders vs. 2/38 IUD infants No differences reported in adverse events or psychomotor development (>60% infants in both groups had resp. disorders, and >30% in both groups had skin disorders)	Strengths: –Long-term follow-up of infants to childhood Weaknesses: –No information on contraceptive switching or discontinuation –Methods to assess psychomotor development not stated –Infant illness by maternal report only –Response rate for study inclusion not stated –Sample size chosen based on WHO recommendations for toxicology, not for BF or health outcomes	Level II-2, Fair Key Question 1
Brito et al., 2009 [20] FAPESP CNPq *Newly identified*	RCT (open label) Brazil *N*=40 women with BMI<30, ages 18–35 years	24–48 h following delivery: 20=Etonorgestrel implant (ETG) 6 weeks PP: 20=150 mg DMPA	BF performance (duration of exclusive BF) Infant growth (weight) Maternal health (outcomes not reported here) Follow-up 12 weeks	BF outcomes No difference in exclusive BF between groups at 6 weeks or 12 weeks: (6 weeks 95% ETG, 85% DMPA; 12 weeks 85% ETG, 75% DMPA) Infant outcomes *Growth* No differences at 6 or 12 weeks	Strengths: –Randomization methods appropriate –Allocation concealment appropriate –Methods clearly described Weaknesses: –Short follow-up –Small sample size with no power calculations	Level I, Fair Key Question 2
Chen et al., 2011 [22] Anonymous foundation *Newly identified*	RCT (open label) United States *N*=96 women interested in PP IUD	Immediate postplacental: 50=LNG-IUD 6–8 weeks PP (delayed): 46=LNG-IUD	BF performance (initiation, duration) Follow-up 6 months	BF outcomes: *Initiation* 32/50 (postplacental); 27/46 (delayed) p=.59 *Duration* 5 weeks (postplacental); 8.5 weeks (delayed) p=.06 *Any BF at 6 months* 3/50 postplacental, 11/46 delayed p=.02 *Exclusive BF at 6 months* 1/50 postplacental, 6/46 delayed p=.05	Strengths: –Randomization methods appropriate –Allocation concealment appropriate –Methods clearly described Weaknesses –6 members of delayed group got interim DMPA prior to LNG-IUD placement –Short follow-up	Level I, Fair Key Question 2

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
					–Very low rates BF in both groups may limit generalizability	
Gurtcheff et al., 2011 [23] National Center for Research Resources *Newly identified*	RCT (open label) United States *N*= 69 peripartum women desiring ETG implant	Insertion at 1–3 days PP: 35=ETG implant (early) 4–8 weeks PP 34=ETG implant (standard)	BF performance (time to lactogenesis stage II, lactation failure, formula supplementation) Follow-up 6 months	BF outcomes *Mean time to lactogenesis stage II* 64 h (early); 65 h (standard) *Lactation failure* 1/34 early, 0/35 standard, risk difference 0.03 (early vs. standard) *Formula supplementation* No difference between groups at 2 weeks, 4–8 weeks, 3 months or 6 months	Strengths: –Randomization methods appropriate –Allocation concealment appropriate –Methods clearly described –Power calculations presented Weaknesses: –32% (11/34) women randomized to standard insertion did not receive implant; as a result analyses are per-protocol	Level I, Fair Key Question 2
Costa et al., 2012 [26] FAPESP *Newly identified*	Cohort Brazil *N*=82 PP women	6 weeks PP: 28=POCs (DMPA, POP, LNG-IUD) 54=NH (Barrier, LAM, TL, Cu-IUD)	BF performance (exclusive and total BF duration) Follow-up 6 months	BF outcomes *Exclusive:* Mean duration 137 days NH, 113 days POC (p=.143) *Total (any BF):* 183 days NH, 183 days POC (p=.383)	Strengths: –Included primiparas –Clear description of methods Weaknesses: –No separate analysis of different POCs –BF outcomes were secondary outcomes	Level II-2, Fair Key Question 1
Espey et al., 2012 [21] ACOG contraceptive grant and University of New Mexico *Newly identified*	RCT (double blinded) US *N*=127 women ages 15–45 years, planning to BF and use oral contraceptives	2 weeks PP: 64=COC (0.35 mg ethinyl estradiol, 1 mg norethindrone) 65=POP (norethindrone 0.35 mg norethindrone)	BF performance (BF continuation at 8 weeks, 6 months; supplementation at 8 weeks) Infant growth (weight, length, head circumference) Follow-up 6 months for BF outcomes, 2 months for infant outcomes	BF outcomes: No difference in continuation at 8 weeks (64% COC, 63.5% POP) or over 6 months (survival analysis); no difference in supplementation at 8 weeks (percents not reported) Infant outcomes *Growth* No difference through 8 weeks	Strengths: –Included primiparas –Randomization methods appropriate –Allocation concealment appropriate –Methods clearly described –Double-blinded –Minimal method switching –Loss to follow-up similar between groups Weaknesses –Small sample size –Short follow-up for infant outcomes	Level I, Fair Key Question 1
Matias et al., 2012 [16]	Cohort Peru	By 72 h By 1 month PP:	BF performance (exclusive BF at	BF outcomes: Women initiating	Strengths: –Clearly described	Level II-2, Fair

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
NIH, Fogarty International Center, NICHD, UC Davis *Newly identified*	*n*=117 PP women planning to exclusively breastfeed	19=DMPA By 3 months PP: 41=DMPA By 6 months PP: 45=DMPA	3 months and 6 months PP) Follow-up 6 months	DMPA after 72H PP had higher odds of exclusive BF at 3 months than those who initiated before 72 h or those who did not initiate at all (adjusted OR 6.1, CI 1.7–21.4 — unpublished data) *DMPA initiation by 1 month PP:* Mos PP / DMPA user exclusively BF (%) / Non-users exclusively BF (%) / P 3 / 79 / 71 / NS 6 / 44 / 33 / NS *DMPA initiation by 3 month PP:* Mos PP / DMPA user exclusively BF (%) / Non-users exclusively BF (%) / P 3 / 85 / 65 / Sig 6 / 38 / 33 / NS *DMPA initiation by 3 month PP:* Mos PP / DMPA user exclusively BF (%) / Non-users exclusively BF (%) / P 3 / 78 / 68 / NS 6 / 29 / 40 / NS Multivariate model: DMPA use by 3 months associated with adjusted RR of exclusive BF at 3 months 1.35 (1.1–1.66)	methodology –Appropriate analytic methods Weaknesses: –Unclear when within the time frame method was started –Unclear what methods, if any, non-were used by non-DMPA users	Key Questions 1 and 2
Brownell et al., 2013 [25] No funding *Newly identified*	Cohort (retrospective) US *N*=183 women who initiated BF	1st 5 days PP: 68=DMPA 115=No DMPA	BF performance (continuation)	BF outcomes: *Median duration* DMPA 30 days, no DMPA 41 days (HR 1.14, nonsignificant) *Continuation at 2 week* No difference between groups on survival curve (p=.24) *Continuation at 6 weeks* No difference between groups (HR 1.22, p=.42) Insufficient events after 6 weeks to draw conclusions	Strengths –Power analysis done (but post hoc) –DMPA exposure verified through hospital records –Survival analysis methodology Weaknesses –Few women in either group continued BF after 6 weeks –Unclear if women in non-DMPA group were exposed after 5 days to either DMPA or to other contraceptives	Level II-2, Fair Key Question 1

Author, year, source of support	Study design, location, population	Interventions	Outcomes, follow-up duration	Results	Strengths/weaknesses	Quality grading/key question
Bahamondes et al., 2013 [24] FAPESP, Conselho Nacional de Pesquisa *Newly identified*	Prospective cohort Brazil *N*= 40 multiparous women with prior BF experience	Day 42 PP: 10=COC 10=ETG implant 10=LNG-IUD 10=Cu-IUD	BF performance (duration, number of episodes/day) Infant growth (weight, height, tibial length) Infant salivary deuterium (data not presented) Follow-up 3 weeks (growth outcomes); 6 months (BF outcomes)	BF outcomes: No significant difference among groups in continued BF at 6 months (data not shown) Significantly more BF episodes day 4 of study in ETG vs. Cu-IUD; otherwise no difference (data not shown) Infant outcomes No significant difference in weight or height change from days 42–63; significant difference in increase in tibial length (0.6 cm vs. 1.3 cm) in ETG vs. Cu-IUD, otherwise no significant difference	Strengths: –Frequent data collection –Clear l y described methodology Weaknesses: –Short follow-up (other than BF duration measure) –Small sample size with no power calculations reported	Level II-2, Poor Key Question 1
Singhal et al., 2014 [27] Not stated *Newly identified*	Prospective cohort India *N*=250 women who initiated BF	Days 3–10 PP: 150=DMPA (only 100 with full follow-up) 100=NH	BF performance (duration, number of episodes/day) Infant growth (weight, length) Infant health (episodes of diarrhea, URI, fever, rash) Follow-up 6 months	BF outcomes: No significant difference between groups in frequency/continued BF at 6 weeks or 3 or 6 months Infant outcomes No significant differences between groups in weight or length gain at any time point No significant differences between groups in illnesses	Strengths –Included primiparas –DMPA exposure verified Weaknesses –High LTFU and no information provided on DMPA users who failed to provide 6 months follow-up (50/150) –Comparison group poorly described; unclear which NH methods were used –No power calculations reported	Level II-2, Poor Key Question 1

Abbreviations: ACOG: American College of Obstetrics and Gynecology; BF: breastfeeding; CEBRE: Center for the Study of Reproductive Biology; FAPESP: Fundação de Amparo à Pesquisa do Estado de São Paulo; NET: norethisterone; NH: nonhormonal; PP: postpartum; TL: tubal ligation.